

Psychopharmacology of topiramate: from epilepsy to bipolar disorder

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Abstract: Topiramate (TPM) is one of the novel antiepileptic drugs and exhibits a wide range of mechanisms of action. Efficacy of TPM has been demonstrated in partial-onset seizures and primary generalized seizures in adults and children, as both monotherapy and adjunctive therapy. More recently, TPM has been proposed as an add-on treatment for patients with lithium-resistant bipolar disorder, especially those displaying rapid-cycling and mixed states. This paper reviews the multiple mechanisms of action and the tolerability profile of TPM in the light of its therapeutic potential in affective disorders. Studies of TPM in bipolar disorder are evaluated, and the efficacy and tolerability issues as a mood stabilizing agent are discussed.

Keywords: topiramate, antiepileptic drugs, epilepsy, mood stabilizer, bipolar disorder

Introduction

Topiramate (TPM) is a sulfamate derivative of fructose, structurally unrelated to existing anticonvulsants (Perucca 1997; Privitera 1997; Glauser 1999; Reife et al 2000; Shank et al 2000). It was marketed for the add-on treatment of patients with drug-resistance partial epilepsy (Shank et al 1994) and, through the following years, it has shown a broad spectrum of efficacy, which extends to refractory partial and secondary generalized seizures (Faught et al 1996; Privitera et al 1996), primary generalized tonic/clonic seizures (Biton et al 1999) and tonic/atonic seizures associated with the Lennox-Gastaut syndrome (Sachdeo et al 1999; Mikkeloff et al 2003). Preliminary data suggest that, in addition to its use in epilepsy, TPM may have therapeutic effects in some neuropsychiatric conditions, such as bipolar and schizoaffective disorders, bulimia, neuropathic pain syndromes, migraine and cluster headache prophylaxis, and essential tremor (Kamin 2002; Spina and Perugi 2004; D'Amico et al 2006). The variety of proposed clinical applications of TPM is consistent with the multiple mechanisms of action. These mechanisms will be shortly reviewed in the present paper, together with the psychotropic effects of TPM therapy in both epileptic and non-epileptic patients.

Mechanisms of action of topiramate

Preclinical studies designed to elucidate the mechanisms of action of TPM have revealed a broad spectrum of pharmacological properties (Shank et al 2000; White 2002).

Blockade of voltage-dependent sodium channels

TPM reduces the frequency of activation of voltage-sensitive sodium channels in a state- or use- dependent manner. In electrophysiological studies of cultured hippocampal neurons, TPM, at micromolar concentrations, has been found to reduce the duration of spontaneous epileptiform bursts of neuronal firing and the frequency of action potentials elicited by a depolarizing of electrical currents (Coulter et al 1993; De Lorenzo et al 2000). TPM produces a voltage-sensitive, use-dependent,

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